

## Responding to an urgent mental health crisis

Challenges and solutions for people suffering with treatment-resistant depression

### A White Paper from COMPASS Pathways

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### **Foreword** from **George Goldsmith**, CEO and Co-founder, COMPASS Pathways

This White Paper "Responding to an urgent mental health crisis", first published in 2020 and now updated with new content, explores the tremendous challenge of today's mental health crisis, with a particular focus on the millions of people suffering with "treatment-resistant depression". We originally wrote the Paper because we wanted to highlight the urgent problems that exist in today's mental health care, and find some solutions.

A lot has changed in a year. Even before COVID, we were seeing a rapid increase in mental health illness on a global scale, and the pandemic is having a profound impact. According to the Centers for Disease Control and Prevention, more than 40% of adults in the US experienced symptoms of anxiety or depressive disorders at some point between August 2020 and January 2021\*.

And yet, the pandemic has also driven positive change, for example with vaccines coming through clinical trials and regulatory approval - and getting to patients - in record times. COVID has changed attitudes and behaviors in telemedicine and it has begun to open up conversations about mental health and how we care for those who feel they have run out of options.

One of the most promising areas of new therapies for depression and other mental health challenges is the emerging field of psychedelic therapy. In psilocybin therapy alone, there are now more than 20 clinical studies underway to determine the therapeutic potential of psilocybin, including our large-scale phase IIb trial which is expected to report results in late 2021. In April this year, the New England Journal of Medicine published a small study conducted by Imperial College London, in which psilocybin therapy was compared with an antidepressant for the first time. The study showed signals of positive activity in COMPASS's COMP360 psilocybin compared with the standard antidepressant escitalopram, for major depressive disorder.

In the political arena, psilocybin has now been decriminalized in Oregon; Ann Arbor, MI; Denver, CO; Oakland, CA; Santa Clara, CA; and Washington, DC, marking a continued shift in public opinion. A legalization measure has been passed in Oregon, kickstarting a two-year development program looking at how to bring psilocybin to people in supervised, licensed facilities. While we welcome the growing interest in psilocybin and its potential, our focus remains firmly on helping those with serious mental health illnesses, rather than on making psychedelic therapy available to everyone. As such, we continue to believe that the regulatory route of bringing psilocybin therapy through rigorous clinical trials and having it reimbursed through health systems, is the best way to ensure access to this therapy to as many of these patients as possible.

Since we wrote the White Paper, we have been using it as a springboard for discussion, through a series of roundtables with leaders from across the healthcare spectrum, including payers and providers as well as professional association executives and policymakers. As a result of these collaborations, action plans are being developed on topics such as training the mental health workforce, instituting value-based care in mental health, and measuring patient outcomes in mental health. We will be continuing these conversations as we advance our mission of accelerating patient access to evidence-based innovation in mental health, by developing safe, effective and reimbursable options for patients. We hope the White Paper stimulates further thinking and debate; do please get in touch if you have ideas to share on how we can do more to respond to this urgent mental health crisis.

George

## Introduction

Every 40 seconds, someone in the world dies from suicide. And in that time, 20 more people attempt suicide<sup>1</sup>.

We are in the middle of a mental health crisis. Inadequate treatments and care have led to continued suffering for patients and their families, as well as a significant burden on society and healthcare costs. While new therapies are on the horizon, it is unclear how and to what extent these treatments will reach the individuals who might benefit from them. On top of this, the COVID-19 pandemic will continue to challenge our mental resilience and is already having a serious impact on mental health.

This White Paper looks at depression, one of the most prevalent and rapidly growing mental illnesses, with a specific focus on treatment-resistant depression (TRD). It assesses the current state of mental health care in the United States, and calls on all those involved in providing this care – researchers, developers, regulators, healthcare professionals, payers, policymakers – to take a fresh and collaborative approach, and embrace new technologies and innovation, to address the urgent unmet need of depression.

## Executive summary\*



#### Treatment-resistant depression is a growing epidemic

Demand for mental health care services is growing rapidly, with 56% of the US population seeking or wanting to seek help for themselves or for a loved one. There are 17 million people in the United States who suffer with major depressive disorder (MDD) and five million of these have treatment-resistant depression (TRD), which means they are not helped by commonly available treatments. TRD has a wide social impact as such patients are more likely to be suicidal, unemployed, less productive at work, and to experience a significantly higher number of life years lost to disability. On average, the healthcare-related cost of treating a TRD patient is around \$17,000-25,000 a year – about twice that of a non-TRD MDD patient. This is putting significant strain on the Medicare and Medicaid programs, as well as on commercial payers.



## Existing treatments and care pathways do not work for enough people

Over one third of patients with depression do not receive any mental health care. This is due, in part, to multiple barriers to access, including a limited mental health workforce. Among those who do receive treatment, existing therapies are often inadequate. Medication provides some relief to many but doesn't work well for up to 50% of MDD patients and can deliver significant side effects. Psychotherapy can be helpful but takes a long time to work and remains ineffective for over half of MDD patients. There are more resource intensive and invasive brain treatments, like electroconvulsive therapy, transcranial magnetic stimulation, vagal nerve and deep brain stimulations. While they can deliver some benefits, the durability of their effect starts fading after a few months and some carry significant safety concerns (eg short term memory loss with electroconvulsive therapy).

The complexity and cost of researching and developing new treatments for depression, as well as reimbursement pressures, are significant disincentives to invest in this space. Trial initiations for new therapeutics are down 50% over the last decade, and MDD drug candidates represent only 0.2% of the global drug pipeline. We urgently need to reverse this trend and find ways to incentivize and support any innovation that can help the millions of people who are suffering.

## Executive summary\*



## A new wave of promising research offers hope to patients suffering with depression

Recent advances in neuroscience, psychopharmacology, psychotherapy, and technology, open opportunities for an entirely different model of care for depression - one that is more accessible and affordable, evidence-based, preventive, and personalized yet scalable. As researchers gain a deeper understanding of the biology and pathophysiology of depression, a range of rapid acting, potentially more durable and cost-effective treatments with new mechanisms of action are being investigated. Over the last few years, excitement has been building around psychedelic therapies, which are being re-evaluated for therapeutic use under a more integrative paradigm of care that combines medicine with psychological support. This promising research requires a fundamental change in how we deliver mental health care to patients.



## Extensive systemic changes in mental health care are needed to bring innovation to patients and improve outcomes

Existing payment models, clinical guidelines and delivery systems, as well as traditional regulatory pathways and trial designs, are inadequate for the major transformation that is needed in mental health care. Regulators, payers, healthcare professionals, researchers, developers, and providers need to work in close collaboration with one another, and with patients, to develop more patient-centric, evidence-based, and technology-enabled care models. At the same time transformational solutions need to be incentivized and scaled more guickly; regulatory innovation needs to be accelerated; and reimbursement and payment models have to be more effective. The healthcare workforce needs to be expanded; digital technology must be developed to support healthcare professionals and improve patient experience and access; and high-quality data should be collected and shared to deliver more personalized, predictive and preventative care. All this is possible and will improve patient experience and outcomes, while reducing the burden on healthcare systems. It is critically important that any innovation, eg psilocybin therapy, is evidence-based and brought safely to patients suffering with a diagnosed mental health illness via a medically regulated route, not a legalization path.

This paper calls upon everyone involved in delivering mental health care to work together urgently to modernize and transform the system so that it meets the significant unmet needs of its patients.

## Part I: Treatment-resistant depression background and challenges

The impact of mental illness on society is significant. Depression stands out: in the United States, a 2018 study showed the prevalence of depression increased from 6.6% to 7.3% of the population between 2005 and 2015<sup>2</sup>. Results of an April 2020 survey suggest that prevalence of depression symptoms in the US was more than threefold higher during COVID-19 compared with before the COVID-19 pandemic<sup>3</sup>. It is estimated that over 30% of patients are not helped by first- and second- line treatments<sup>4</sup>. A lack of response to two or more adequate treatments for depression is labelled treatment-resistant depression (TRD) and affects around five million patients in the US.

#### This section:

- Defines major depressive disorder (MDD) and treatment-resistant depression (TRD)
- Articulates the burden and impact of TRD

### Mental health disorders

Mood and anxiety disorders are among the most common psychiatric diagnoses, affecting roughly 20% of the adult population in the US<sup>5</sup>. Many factors contribute to precarious mental health, ranging from environmental to genetic, and substantial challenges exist in the diagnosis and treatment of mental health conditions. Poor mental health can affect behavior, emotion and cognition, and result in decreased quality of life and day-to-day functioning.

Mood disorders are characterized by depressed mood, disengagement from family and social interactions, lack of energy and interest in enjoyable activities, feelings of guilt or worthlessness, slowing of movements and, in some cases, suicidal thoughts and behaviors. Depression and bipolar disorders are among the most common and debilitating mood disorders for both patients and caregivers (see Appendix A).

While the causes of many mental health disorders are not fully understood, scientists generally agree that an imbalance of neurotransmitters ("chemical messengers") preventing healthy communication in the brain can play a key factor. However, 50 years of therapeutic research based on this hypothesis has not resulted in any reduction in the incidence or prevalence of depression. New approaches are badly needed.

Around 40% of people with a mental health condition have co-morbid illness and poor outcomes in mental health have implications for physical health and wellbeing<sup>6,7</sup>. Half of those with chronic ill-health, such as cancer and Parkinson's disease, develop depression, and mental disorders are a risk factor for developing chronic illness<sup>8</sup>. The symptoms of mental disorders often contribute to self-harming behaviors such as smoking and substance abuse.

High rates of mental illness are associated with poverty and homelessness: 39% of people with serious mental illness have an annual income below \$10,000 compared with 23% of people

without a mental illness<sup>7</sup>. This population also experiences higher rates of homelessness: over 60% of people who are chronically homeless have experienced a serious mental health challenge at some point in their lifetime<sup>9</sup>. Moreover, roughly 20% of the incarcerated population have a mental health condition<sup>10</sup>.

### Depression: an overview

Depression is a challenging mood disorder because of its prevalence, episodic nature, and varied way in which it manifests itself. In the US, about 17 million adults (7% of all adults) and three million children (13% of all children) aged 12 to 17 years had at least one depressive episode in 2019<sup>11</sup>. The lifetime prevalence of depression is approximately 20% which means that one in five adults will experience a depressive episode at least once in their lifetime<sup>12</sup>.



Figure 1.1: Past year prevalence of major depressive episode among US adults

NH/OPI\*\* = native Hawaiian/other Pacific Islander AI/AN\*\*\* = American Indian/Alaskan native 2 or more = multiracial/mixed race

A combination of genetic, biological, environmental, and psychological factors contributes to the development of depression. Risk factors can range from having a blood relative who has suffered from depression at some point, to experiencing major life changes or a traumatic event, having a chronic physical health condition, or abusing substances such as alcohol or drugs<sup>11,14</sup>. Individuals with depression may have altered levels or impaired functioning of the neurotransmitter serotonin, which guides mood, hunger and sleep. Lower levels of serotonin (sometimes caused by problems with a neurotransmitter called glutamate) may cause feelings of sadness or hopelessness for extended periods of time, lack of interest in activities, difficulty sleeping and changes in appetite<sup>15</sup>. Recently, an impairment in glutamate has also been hypothesized, leading to the development of a new generation of antidepressants, including esketamine (SPRAVATO™).

Depressive episodes can vary in severity and duration. Without treatment, symptoms can progress to having a significant impact on daily life and functioning. In its most severe form, individuals experience depressive symptoms that can lead to life-threatening consequences<sup>16,17</sup>.

## Major depressive disorder and treatment-resistant depression

Major depressive disorder (MDD) consists of depressive episodes that can be mild, moderate, or severe, making it difficult for some patients to attend school or work, or care for themselves<sup>14</sup>.

MDD is the leading cause of disability nationwide<sup>18</sup>. Prevalence of depression is higher in government programs for seniors and people living in poverty: in the Medicare program approximately 21% of adults over the age of 65 have MDD, while 25% of Medicaid enrollees do<sup>19,20</sup>.

In some cases, repeated attempts to treat the disorder fail to help patients, leaving them with persistent and adverse symptoms, and those who do respond to treatments have a higher risk of relapse and further depressive episodes<sup>21</sup>. Depression that isn't helped after two or more adequate anti-depressive treatments is referred to as treatment-resistant depression (TRD).

TRD affects five million people in the US. There is a 20-30% prevalence of TRD among patients with MDD<sup>22,23</sup>. Of Medicaid enrollees with MDD, approximately 26% have TRD<sup>20</sup>.

TRD patients face issues of misdiagnosis, prolonged depressive periods, co-occurring mental and physical disorders, and longer periods of time with a lower quality of life than patients suffering with less severe depression. About half of TRD patients are unable to perform daily tasks and experience a much lower quality of life<sup>13</sup>. They have lower work productivity, higher rates of unemployment and are more likely to receive disability or welfare benefits<sup>24</sup>. Employment rates for this population range from 55% to 63%, compared with an employment rate of 76% for those without a mental disorder<sup>25</sup>. Employees suffering with TRD have higher rates of absenteeism compared with those without a mental disorder: 26.9 days vs 16.7 days<sup>13,26</sup>. Co-occurring disorders are also common in TRD patients, who suffer to a greater extent from joint, limb or back pain (73% vs 70% for those without TRD), cardiovascular disease (56% vs 49%), and delusions and other psychotic symptoms (13% vs 6%), in comparison with treatment-responsive patients suffering with MDD<sup>27</sup>.

### Suicide and treatment-resistant depression

Suicide mortality is a significant and rapidly growing public health burden. Worldwide, nearly 800,000 people die from suicide every year, that is one person every 40 seconds, and for each adult who dies by suicide, there may have been more than 20 other attempts<sup>1,28</sup>. Suicide ranks as a top 10 leading cause of death in the US and is a leading cause of death in young adults. In 2019 alone, 47,511 lives were lost to suicide<sup>29</sup>. Risk of suicide increases with severe and persistent mental disorders<sup>30</sup>. Approximately 90% of individuals who die from suicide in the US have an underlying mental illness, and about half of those suffer with MDD<sup>31,32</sup>. According to Mental Health America, since the COVID-19 pandemic began to spread rapidly

Increasing suicide rates in the US are a public health crisis and the lack of high-quality treatment for major depression and treatment-resistant depression continues to contribute to that crisis.

> Andrew Sperling, National Alliance on Mental Illness

in March 2020, over 178,000 people have reported frequent suicidal ideation. More than 35% of those surveyed reported having thoughts of suicide more than half or nearly every day of the previous two weeks in September 2020<sup>33</sup>.

TRD patients are more likely than the rest of the population to have suicidal tendencies, ranging from chronic suicidal ideation to suicidal intent and attempts, that can lead to hospitalization, and in some cases, death<sup>27</sup>. Research conducted in 2018 suggests that as many as 30% of patients suffering with TRD attempt suicide at least once during their lifetime<sup>34,35</sup>.

### Mental health care spending and use of services

Annual spending on mental health care in the US is roughly \$200b - around 5% of total healthcare spending. It includes payment for drugs, inpatient and outpatient treatments, as well as integration of behavioral healthcare into primary care, ambulance services, community centers, and grants that offer supported employment, housing, rehabilitation services and jail diversion programs<sup>36</sup>. Medicaid and Medicare are the primary payers for these services, with the private sector picking up about a quarter of costs<sup>37</sup>.

Figure 1.2 displays the distribution of spending by payer for mental health care over the last 34 years. Of note:

- Between 1986 and 2020, total expenditure on mental health grew from \$32b to \$238b, a 650% increase
- The share of public payers in total mental health expenditure has remained stable over that same period at roughly 60%, yet the role of the federal government in covering populations with mental health disorders has grown
- Medicare and Medicaid represented 6% and 17% of spending in 1986, this grew to 15% and 30% in 2020



#### Figure 1.2: Distribution of mental health spending by payer, in 1986, 2009, 2014, and 2020\*

Turning to costs for MDD and TRD, figure 1.3(a) shows that:

- The estimated average annual healthcare costs for all TRD patients are about \$17,000, at least 1.7 times higher than for non-TRD MDD and more than three times higher than for non-MDD
- On aggregate, non-mental health-related costs are higher than mental health-related costs, suggesting that TRD patients have more co-morbidities (higher morbidity and mortality)
- Inpatient and outpatient costs are the highest drivers of direct costs among MDD patients, while pharmacy cost is relatively low



Source: Amos et al, 2018<sup>38</sup>

Graph showing direct healthcare cost associated with MDD (non-TRD), non-MDD (a patient without depression) and TRD. Direct costs include inpatient, emergency department (ED), outpatient, and other costs eg medical ancillary services. Adjusted for baseline total healthcare costs and Quan-CCI. P values and confidence intervals were obtained using a nonparametric bootstrap procedure

\*Significance at the 5% level

Abbreviations: CI=confidence interval, PPPY= per patient per year, Quan-CCI=Quan-Charlson Comorbidity Index<sup>38</sup>

## Figure 1.3(b): Direct mental health related costs between TRD and non-TRD MDD patients (PPPY in US\$2015)<sup>38</sup>



Within mental health care costs, depression-related cost occupies the largest proportion, while suicide-related cost is relatively low. Other mental health-related costs are related to mental health co-morbidities (figure 1.3(b)).

Notably, patients with TRD fill over two times as many prescriptions as non-MDD patients<sup>39</sup>. Other research shows the per person costs for TRD can be even higher – closer to \$25,000 – for the highest risk populations due to additional prescriptions, doctor and psychiatrist visits, and increased rates of hospitalization<sup>14</sup>.



#### Figure 1.4: Cost comparison of non-TRD MDD and TRD patients in the US

In government-funded healthcare programs, TRD adds significantly to cost pressures. Costs for Medicare beneficiaries with TRD were 1.5 times higher than for those with non-TRD MDD in 2014 (see figure 1.4). For the Medicaid program, the costs for an enrollee with TRD were \$18,000 a year, 1.6 times higher than for those with non-TRD MDD.

In conclusion, the burden of depression, and specifically TRD, on healthcare systems and society, is significant. Rates of diagnosis for TRD are growing more than 10% per year, resulting in increased suffering for patients and their families, as well as in rising costs and pressure on government programs, health systems and employers<sup>40</sup>. A closer look at the treatment landscape will help to identify gaps in care and ways to design solutions for this growing epidemic.

# Part II: Current approaches and limitations for treatment of depression

Over the last few decades, treatment approaches for depression have hardly changed, with an over-reliance on a few classes of antidepressant medication. There has been little innovation in care delivery, and healthcare access challenges remain, with over one third of US adults with MDD not receiving any mental health care at all<sup>11</sup>.

#### This section:

- Outlines the fragmented delivery system for people with depression
- Describes the mechanisms and limits of the three main treatments for depression: psychotherapy, drug therapy and physical (or somatic) therapy
- Concludes that the current mental health care system provides sub-optimal patient care

## A fragmented and inaccessible mental health care system

Less than half of US adults with MDD receive the recommended levels of care and many patients with depression do not receive any care at all<sup>41</sup>. Of US adults with MDD in 2017, 44% received combined medication and health professional treatment (where the health professionals can administer treatment), 15% health professional treatment only, 6% medication only, and 35% no care at all<sup>11</sup>.

The current delivery model for treating mental health disorders is fragmented, with limited and variable access to hospitals, residential facilities and community mental health centers. Today's delivery system reflects a transition from a past model where state mental health hospitals provided long-term inpatient treatment for nearly half a million patients with mood and psychotic disorders. Cultural and political shifts, beginning in the 1950s, led to the deinstitutionalization movement, which offered opportunities to treat patients in less restrictive environments and enabled them to live in their own homes and communities. Stakeholders in the mental health community supported this move and developed new systems of care<sup>42-46</sup>, but needs and costs for residential care remain high<sup>47</sup>.

Demand for mental health care services is growing rapidly, with 56% of the US population seeking or wanting to seek help for themselves or for a loved one, according to a recent survey<sup>48</sup>. However, 75% of those surveyed said these services were not accessible for everyone, and 47% believe options are limited. Findings from the survey show the following barriers make it difficult to access mental health treatment:

• Lack of awareness: Of those surveyed, 29% wanted to access help but did not seek treatment for themselves or loved ones, due in part to not knowing where to go; 21% wanted to see a professional but were unable to for reasons outside their control\*

- Limited options and long waiting times: Access to face-to-face services is a higher priority for Americans seeking mental health treatment than access to medication; 38% say they have had to wait longer than one week for mental health treatments, and 46% have had to, or know someone who has had to, drive more than one-hour roundtrip to seek treatment
- High cost and insufficient insurance coverage: Cost and poor insurance coverage were cited by 42% as the top barriers to accessing mental health care; 25% reported having to choose between getting mental health treatment and paying for daily necessities

We must reimagine our health system to ensure that every American has access to the care they need, when they need it. Certified Community Behavioral Health Centers represent a long overdue shift to integrate physical and mental health care, changing the way services are provided and ensuring greater equity. S

Chuck Ingoglia, National Council for Mental Wellbeing

 Social stigma: Stigma was an issue for 31% who worried about being judged when they told others they had sought support from mental health services; 21% have lied to avoid telling people. This stigma is particularly strong for younger Americans: 49% Generation Z vs 40% Millennials vs 30% Generation X vs 20% Boomers are more likely to have worried about others judging them<sup>48</sup>

Even when individuals manage to access care, they face a system ill-equipped to address their challenges. Burdens of care fall on an overstretched primary care system where professional training and support for patients with mental health disorders are limited. Patients often do not get the recommended levels of care and oversight of use of prescription drug regimens, and adherence suffers as a result. About 75% of patients with depression are treated by primary care providers, yet only 35% to 50% of patients with MDD are detected, and fewer than 22% who are diagnosed receive adequate care and treatment<sup>49</sup>.

Beyond the primary care sector, there is another shortage of adequately trained mental and behavioral health clinicians to deal with this mental health crisis. According to the Department of Labor's Bureau of Labor Statistics, there are 577,000 mental health professionals practicing in the US today<sup>50</sup>. Since 2011, this number has grown only 4% while mental health diagnosis rates have risen in the double digits. While the number of clinical and counselling psychologists has grown 23% to around 170,000 in 2017, the number of psychiatrists has declined 36% to 25,000. Mental health and substance abuse social workers now number around 112,000, a 23% decline<sup>50</sup>.

Paying for mental health care can be cost-prohibitive for people without insurance<sup>51</sup>. Because Black, Hispanic and low-income individuals have higher rates of uninsurance compared with middle-to-high income white counterparts, barriers to access exist for those groups. Medicaid is the primary payer for behavioral health and home- and community-based services for lowincome people. However, even those with Medicaid or other insurance can face challenges receiving appropriate mental health care because of limited networks, high cost-sharing, lack of mental health benefits parity in health plans, or other factors. Studies have found that when broad insurance coverage increases (ie Medicaid expansion), access to mental health care services also increases but disparities may remain<sup>52</sup>. Even for those who are insured, access may be limited. According to a 2014 study published in JAMA Psychiatry, only about 55% of psychiatrists accepted private insurance, significantly lower than the almost 89% of physicians of other specialties<sup>53</sup>. Lower rates of network participation translate to a higher likelihood of out-of-network care with higher out-of-pocket costs. In fact, according to a recent claims database study, on average, those with mental health conditions paid \$341 more than those with diabetes<sup>54</sup>.

Increasingly, experts are looking at the impact of socio-economic factors on health outcomes. These social determinants of physical and mental health include resource-related deficiencies in employment The most impactful way to improve mental health is to optimize public health policies at all levels, and alter social norms and cultural biases across all sectors of society. This places greater value on giving everyone an equal chance at living a fulfilling and healthy life.

> Michael Pollock, Depression and Bipolar Support Alliance

and income, education, housing, nutrition, and transportation. Family and community dynamics and relationships, housing quality, social supports, and work and school conditions<sup>55</sup>, can all impact treatment success and are often ignored in clinical program design<sup>56</sup>. The World Health Organization (WHO) states that "risk factors for many common mental health disorders are heavily associated with social inequalities, whereby the greater the inequality the higher the inequality in risk"<sup>56</sup>.

Integrated approaches where mental health services are coordinated with other medical services are beginning to be considered, but treatment for many mental health disorders are still predominantly focused on pharmacological interventions. In many cases, drugs can offer relief to patients; however, there are still serious concerns about overuse and misuse of complex drugs, and management of side effects without appropriate physician oversight.

### Treatment approaches for depression

No "silver bullet" exists to address the needs of patients with depression. Clinicians who prescribe different treatment options lack high-quality evidence and all too often have to rely on a trial-and-error approach, course correcting as patients are failed by drugs or experience difficult side effects. Experts are beginning to recommend a shift to more multi-modal treatments (ie a mix of pharmacological and psychological interventions), but a provider-centric and fragmented mental health care delivery system makes it difficult for physicians and patients to embrace a more integrative treatment approach.

Patients suffering with depression currently have two main treatment options: psychotherapy and drug therapy. The first relies on psychological approaches to explore thinking, feelings, and behavior patterns, guided by a trained professional (often a psychotherapist or psychologist) who tries to activate behavioral and cognitive changes and equip patients with tools to manage depressive symptoms. The second relies on a psychiatrist who will prescribe drugs which work on neurotransmitter systems in the brain known to affect mood. Both methods take weeks to yield results. Treatment plans can vary substantially between patients and a recent analysis of real-world data, using more than 250 million medical records of depressed patients from multiple sources in over 10 countries, found that more than 10% of patients follow unique treatment pathways<sup>57</sup>. This does not reflect a personalized approach, but a rather haphazard trial-and-error based system that may not result in the best outcomes for patients.



The inner circle in the figure shows the first relevant medication taken by the patient, the second circle shows the second medication, and so on. SSRIs (Citalopram, Sertraline, Escitalopram, Fluoxetine and Paroxetine) and SNRIs (Duloxetine and Desevenlafaxine) are the most widely prescribed classes of antidepressants. The figure is indicative of data sources from four countries (UK, US, Japan, South Korea).

Patients with TRD are not able to achieve symptom remission despite serial treatment trials. The emphasis of treatment at this point shifts from a goal of achieving remission to optimal symptom control, daily psychosocial functioning and quality of life. Physicians and patients will have to jointly decide which mix of treatment options, including pharmacotherapy, psychotherapy, neurostimulation, is likely to optimize such outcomes. More resource intensive and/or invasive interventions can be considered, such as transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT), deep brain stimulation (DBS) or vagus nerve stimulation (VNS). Figure 2.2 shows that the costs associated with TRD increase following each subsequent line of therapy<sup>58</sup>.



## Figure 2.2: Direct costs among TRD patients stratified by number of lines of therapy of adequate dose and duration (PPPY in US\$2015)

## Psychotherapy

In psychotherapy, a mental health professional helps patients on the path to recovery by addressing maladaptive patterns and enabling change in cognition and/or behavior.

Two of the most common psychotherapies are cognitive behavioral therapy (CBT) and interpersonal therapy (IPT). Both approaches are recommended to be delivered over a 12 to 16-week period and can be combined with drug therapy. CBT is delivered individually (face-to-face or online) or in a group to identify distorted thought and behavior patterns and rectify them. This goal-oriented approach helps patients to develop skills to cope with symptoms and problems, as well as prevent future episodes of depression. IPT tries to improve the quality of relationships in a patient's life and focuses on how relational problems and interpersonal deficits can make someone more vulnerable to depression. It uses relationship skill-building and coping mechanisms to diminish interpersonal consequences and resolve conflict to reduce distress.

Psychotherapeutic approaches are effective for many individuals, but do not work for everyone. They are often seen as a complement to, rather than a substitute for, pharmacological interventions. They require a significant time commitment from patients and their effectiveness relies on the availability of a trained therapist and their ability to deliver the therapy consistently and skillfully. "Good chemistry" between a patient and a therapist (often referred to as "therapeutic alliance") takes time and has a significant impact on outcomes.

One of the biggest downsides of psychotherapy is that it takes a long time to show effectiveness. Many patients report seeing progress after six to 12 visits<sup>59</sup>. Since visits are often weekly or biweekly, this process can take up to 24 weeks. For over half of patients with TRD the first attempt of psychotherapy is ineffective<sup>60</sup> and expert guidelines recommend different psychotherapeutic approaches across the depressive spectrum.

### Drug therapy

Current pharmacological treatments for patients with depression work for many, but not for all. Finding the appropriate medicine or combination of medicines in the context of a treatment plan can be difficult. Physicians usually prescribe commonly used antidepressants and follow a trial-and-error approach, attempting to optimize dose and duration before they augment the existing antidepressant with a second agent, for example an additional antidepressant, or antipsychotic or mood stabilizer. Eventually, patients who are not helped by pharmacological treatments can opt for more invasive and resource intensive in- or outpatient interventions such as brain stimulations (see *physical therapies* below).

There are five main categories of antidepressants available on the market, each with a different mechanism of action. These are: selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), atypical antidepressants, monoamine oxidase inhibitors (MAOIs), and tricyclic antidepressants (TCAs)<sup>61</sup>. All these substances target communication in one or more brain neurotransmitters, chemical messengers in the brain known to regulate mood and depression symptoms. The six neurotransmitters known to play a role in depression are: serotonin, norepinephrine, acetylcholine, dopamine, glutamate and gamma-aminobutyric acid<sup>61</sup>.

Different antidepressant drugs have different side effect profiles. Studies indicate that SSRIs and SNRIs have the fewest side effects and are prescribed more often than other antidepressants; however, they take longer to have an effect, usually between two to four weeks. MAOIs and TCAs are generally less well tolerated<sup>62</sup>.

The main challenges with drug therapies are:

- Failure to achieve remission in many patients, despite several treatment attempts: Over 50% of first attempts with a medication fail, and the second line of treatment fails nearly 75% of the time (figure 2.3), at which point it is highly unlikely that any subsequent drug therapy will be effective, leaving up to 30% of patients as "treatment-resistant"<sup>63</sup>
- Delayed symptom relief: Conventional antidepressants generally do not achieve maximum efficacy until after several weeks, if at all. Dose adjustment or a change in prescription is needed if patients fail to respond to treatment, which causes delays in initiation of the next phase of treatment. The impact of this delay is exacerbated in vulnerable populations who suffer with other health issues. Limited treatment options, delays, and additional costs often deter patients from trying a new therapy that may work for them
- Undesirable or unbearable side effects: Patients often experience side effects from antidepressant medications, weeks prior to experiencing symptom relief. In some cases, this leads them to stop drug treatment altogether. Side effects include nausea, increased appetite and weight gain, fatigue and drowsiness, sexual dysfunction, insomnia, blurred vision, dizziness, agitation, irritability, and anxiety. About 95% of patients taking antidepressants experience some form of side effect at some point in their treatment, with nearly one in four describing side effects as very or extremely difficult to handle<sup>64</sup>
- Suicidal thoughts and condition deterioration: In some cases, worsening depression or suicidal thoughts occur while taking these medications particularly in adolescents and adults under the age of 25 years<sup>61</sup>. Due to this increased risk of suicidal ideation, the US

Food and Drug Administration (FDA) requires the strictest "black box" warning on the label of all antidepressant patient information leaflets. In cases where patients experience severe side effects or adverse events, providers may prescribe additional or alternative medicines. However, the experience of side effects prior to any relief disengages patients in their care, which in turn decreases the value and quality of care<sup>65</sup>

• **Medication non-adherence:** Because of the difficulties with side effects and delays in symptom relief, only 65% of individuals with depression adhere to their prescribed medication, compared with 76% of individuals who have been prescribed a medication for a physical disorder. Severity of depression also impacts adherence: only 50% of individuals with severe depression and psychotic disorders adhere to their medication. Other factors affecting poor adherence include fear of addiction, disbelief in ability to recover, lack of patient education or inadequate follow-up by clinicians<sup>66-68</sup>. The risk of relapse due to poor adherence under a maintenance treatment is relatively high (16% to 24% over a one-year period)<sup>69</sup> and may lead to some psychological dependence<sup>70</sup>



Figure 2.3: Number of MDD patients in the US failing successive lines of treatment

1. Prevalence estimated at 8% (between 5-10% depending on epidemiological study]) of a population of 212 million. 2. All diagnosed MDD patients assumed to recieve first line treatment. 3. Range includes lower bound from NICE relapse rate (July 2018) and higher bound from STAR\*D QID-SR16 remission rates.

### Physical (somatic) therapies

For patients with TRD, who have not been helped by antidepressants, there are few effective options left. These include more resource-intensive and invasive interventions using medical devices delivered under medical supervision in inpatient or outpatient settings. The gold standard for last resort treatment in depression is electroconvulsive therapy (ECT), a procedure that induces a controlled seizure affecting connectivity of neural networks<sup>71</sup>. ECT has been available for decades, is well studied, and has proven to be effective in a subset of patients, but its uptake in clinical practice remains relatively limited. It is delivered under general anesthesia in six to 12 sessions. A minority respond in fewer than six sessions and experience some form of symptom relief. Some patients receive a number of treatments before experiencing any symptom relief. Others require routine "maintenance ECT" every month or every other month<sup>71</sup>. ECT is costly and invasive and can lead to protracted side effects including headache, nausea and confusion, as well as long-lasting memory loss<sup>71</sup>.

Better tolerated brain stimulation approaches have started to enter clinical practice, such as (repetitive) transcranial magnetic stimulation (TMS or rTMS) or intermittent theta-burst stimulation (iTBS). Such interventions can be offered to patients diagnosed with MDD after one or more failed medication attempts<sup>72</sup>. TMS uses electromagnetic coils to stimulate nerve cells in the frontal lobes of the brain<sup>73</sup>. Placement of coils, dosage, and frequency of magnetic energy vary by patient and must be determined by physicians, sometimes informed by imaging techniques like functional magnetic resonance imaging (fMRI), with sessions occurring daily for up to two hours, five days a week, for four to five weeks<sup>74</sup>.

Deep Brain Stimulation (DBS) is a neurosurgical procedure involving the placement of a medical device called a neurostimulator – sometimes referred to as a "brain pacemaker" – which sends electrical impulses, through implanted electrodes, to specific targets in the brain. While its underlying principles and mechanisms are not fully understood, DBS directly changes brain activity in a controlled manner. It is traditionally used for the treatment of movement disorders, including Parkinson's disease, essential tremor, and dystonia. DBS has also been studied in a small number of clinical trials to treat patients with TRD<sup>74</sup>. While evidence is currently insufficient to support DBS as a therapeutic modality for depression, the procedure may be more common in the future<sup>75</sup>.

Building on experiences with ECT and TMS, physicians are also exploring other neurostimulation therapies<sup>76</sup>. One technique specifically focused on TRD and epilepsy is a procedure called vagus nerve stimulation (VNS). It refers to one of the nerves that is responsible for the transmission of messages to the parts of the brain that impact mood. VNS works similarly to pacemakers, where a battery-powered device sends electricity pulses to the vagus nerve. This treatment is only recommended for patients with severe depression and a history of at least two to four failed medication attempts and no response to ECT<sup>77</sup>. Experts recommend additional drug and psychotherapy be continued alongside this therapy as well<sup>77</sup>.

## Lack of research and development for new drug treatments

There is a significant unmet need for new therapies for the treatment of depression. Only 29 active substances have been approved by the FDA for MDD since 1959, and all work on the same hypothesis, ie modulation of the brain's monoamine neurotransmitter levels<sup>78</sup>. New strategies were proposed in the late 1990s and early 2000s, as a result of molecular biology research in the areas of neuroendocrinology, neuroinflammation, and neuroplasticity. However, many of these have been unsuccessful.

Current MDD clinical programs on therapeutic target strategies reveal only nine strategies outside the

 New research is encouraging for the millions of individuals and their families affected by limited treatment options for TRD. Too many lives are cut short by suicide every year.
 We hope more research will provide a better understanding of MDD and TRD, and avoid potential tragic consequences.

> Andrew Sperling, National Alliance on Mental Illness

monoamine strategy, mostly focused on the glutamate systems. There are only a handful of developments that explore the perturbation of brain networks and/or the interconnections of these networks<sup>79</sup>, and these are largely outside the traditional drug development path.

In fact, over the past decades, major pharmaceutical companies have curtailed research and development efforts in this space and few new treatments have been approved since the launch of SSRIs and SNRIs in the early 1990s<sup>80,81</sup>. Promising new therapeutic approaches, based on molecular targets discovered in the 1990s and early 2000s, have experienced a significant number of setbacks. There are currently around 30 drug programs in clinical trials for MDD. Clinical trial initiations for new therapeutics in this field are down 50% over the last decade, and drug candidates for new clinical studies are nearly non-existent. MDD drug candidates represent only 0.2% of the global drug pipeline. Venture investment in companies focused on depression is at record low levels, 10 times lower than in oncology companies<sup>79,82,83</sup>.

Impediments to drug development fall into three broad areas: scientific, regulatory, and

commercial. Scientific hurdles in drug development for depression include a lack of predictive animal models, difficulty delivering and assessing pharmacokinetic profiles in the brain, a low number of targets, and high heterogeneity in the patient population. On the regulatory front, phase III efficacy trials can require enrolling thousands of patients in a single study, making it especially burdensome for small companies. Further, current scale and measurements were designed in the 1950s and '60s and may not be suitable for a new generation of innovative treatments. From a commercial perspective, over 90% of prescribed medicines for depression are generic, and for a new innovative drug to recoup investment with expected risk adjusted returns, it must be superior to those on the market<sup>79,84-86</sup>.

Our community has told us that symptom mitigation is not the highest treatment outcome priority. In a 2018 DBSA survey, 91% of respondents said their health goal is to function as well as possible, and 83% prioritized functioning well at work, at play and in connecting with others.

Phyllis Foxworth, Depression and Bipolar Support Alliance

With limited options in the existing treatment regime, there is a significant need to support transformational research and development programs that will allow promising innovation to successfully advance through clinical research, be approved by regulators, reimbursed by payers, adopted by clinicians, and accessed by patients.

# Part III: Emerging solutions in treatments for depression

After decades of limited innovation, the last few years have seen the emergence of new therapies, technologies and innovative treatment paradigms for depression. Much focus has been placed on improving access to, and the quality of, mental health care, with the combination of pharmacological, psychotherapeutic and technological solutions. As explored above, new options are needed to treat and support people whose depression has not been helped by traditional methods of care.

In addition to the development of compounds with novel mechanisms of action, one of the most exciting areas of development is the repurposing of well-known and naturally occurring substances, and psychedelic substances, under a protocol that combines medicine with psychological support.

#### This section:

- Looks at emerging treatment options for depression and the challenges of getting these to patients
- Describes the renaissance of psychedelic therapies and their potential for the treatment of mental health conditions, especially depression
- Highlights recent efforts to legalize or decriminalize psychedelics, and emphasizes the need to take an evidence-based approach to responsibly and safely develop psychedelic substances into licensed and reimbursed medicines
- Explores how technology and data can improve patient access, experience and engagement with mental health care services

## Emerging treatment options and the challenges of getting these to patients

#### Next generation of antidepressants

As described earlier, the majority of antidepressants in clinical use today act by enhancing the neurotransmission of a particular class of neurotransmitters: the monoamines (serotonin, norepinephrine, dopamine). Given that so many people are not helped by antidepressants, there is a real need for new mechanisms of action, with faster and more durable efficacy, and better side effects and tolerability profiles.

Over the last few years, a number of new pharmacological approaches with different mechanisms of action and a faster onset have been investigated, but largely with disappointing results:

• SAGE-217 by Sage Therapeutics: an oral antidepressant targeting a different neurotransmitter in the brain, the gamma-aminobutyric acid type A (GABA). Brexanolone (Zulresso™) was developed by SAGE and originally approved in 2019 for post-partum depression<sup>87</sup>. The company then developed SAGE-217, an experimental drug for MDD that functioned in the

same way as ZULRESSO. Sage-217 continues to be investigated for multiple indications, including episodic treatment for MDD

- **Rapastinel by Allergan:** an intravenous antidepressant acting as an NMDA (N-methyl-D-aspartate) receptor partial agonist with an agonist activity at the glycine site. Allergan reported negative results in its phase III program in March 2019. Rapastinel was considered the main competitor of esketamine (see below)
- ALKS-5461 by Alkermes: a daily, sublingual antidepressant composed of buprenorphine and samidorphan, acting on opioid receptors. The FDA denied approval in February 2019 and asked for more substantial evidence of drug efficacy
- AXS-05 by Axsome Therapeutics: an oral antidepressant combining bupropion and dextromethorphan, acting on a variety of neuronal receptors (NMDA, sigma-1) and transporters (serotonin and norepinephrine). A new drug application for the treatment of MDD was accepted by the FDA in 2021 and granted priority review

Other investigational compounds for the treatment of depression have failed or been abandoned by their sponsors, including MIN-117 by Minerva, RO-4917523 by Roche and CP-101 by Pfizer. Reasons are mostly related to lack of efficacy and safety concerns, confirming the significant challenges in the clinical development of antidepressant medications.

As noted above, failure rates in depression programs are significantly higher than in other therapeutic areas, for multiple reasons ranging from high placebo response rates to complexity of the underlying pathophysiology.

In a welcome contrast to numerous failures over the past few years, esketamine (SPRAVATO) by Janssen Pharmaceuticals (the pharmaceutical arm of Johnson & Johnson) was approved by the FDA in March 2019 as an adjunctive treatment for TRD.

#### Ketamine and esketamine

Ketamine is an anesthetic that has been used for several decades in sedation, anesthesia and chronic pain, and has gained recent attention as a treatment for depression. It is fast and short acting, and therefore a promising option for immediate relief of depressive symptoms.

There are two forms of ketamine, which have both been studied for depression. Racemic ketamine is currently used off-label as an intravenous injection and is available in private clinics with an average annual cost to patients of \$2,500-5,000<sup>88</sup>. The S-enantiomer of ketamine, esketamine (SPRAVATO), is administered intranasally as a spray and has been approved by regulators in the US and Europe as an adjunctive treatment (given in addition to a primary treatment) for TRD. It needs to be administered regularly (weekly or every two weeks) in a controlled environment and requires active monitoring from a healthcare professional for two hours following each dose intake<sup>89</sup>.

Both ketamine and esketamine block NMDA receptors in the brain, leading to an increase of glutamate, a key activating neurotransmitter, and a subsequent increase in neuroplasticity in the brain. This process seems to allow the brain to create new neural connections and may lead to more positive thoughts and behaviors<sup>90</sup>.

One study indicates that 70% of patients with TRD noticed improvement in their condition with the combined use of esketamine and antidepressants, compared with about half of another study group who received a placebo on top of their antidepressant<sup>91</sup>. Side effects included elevated blood pressure, dizziness, sedation, cognitive impairment and dissociation<sup>92</sup>. The main drawbacks are that the chronic effects of long-term use of esketamine are not yet known, and that ketamine and esketamine are both associated with a high abuse potential<sup>93</sup>.

SPRAVATO and other novel treatments offer new modes of administration, eg nasal spray, intravenous injections, continuous prolonged infusions, which allow for an increase in bio-availability and potential efficacy of the drug. Some of these treatment options, like SPRAVATO and Brexanolone, need to be administered in a controlled environment under medical supervision, requiring new infrastructure, capabilities and changes in workflows. This makes the administration of some treatments more burdensome and costly for providers, raising the costeffectiveness threshold, and limiting clinical adoption and patient access.

### Psychedelic therapies: a new frontier

#### **Renewed** opportunities

One of the most exciting developments in neuroscience research today is the renaissance of psychedelic substances for therapeutic purposes. Recent research suggests that psychedelics offer promising opportunities to treat a range of mental health disorders, including TRD, and researchers are focusing on how to harness the potential of these substances. They have found that many psychedelic drugs may have psychopharmacological effects on the brain (such as number, density and connections of neurons). To an extent, these drugs may affect brain function in the same way that ketamine does.

Natural psychedelic compounds found in mushrooms, cacti and other plants have a long history in medicinal use (see figure 3.1). From the middle of the 20th century, scientists also began developing synthesized drug products with psychedelic effects. Some were synthesized versions of active ingredients, eg psilocybin (an active ingredient in so-called "magic" mushrooms) and mescaline (active ingredient from the peyote cactus). Others were compounds such as MDMA and LSD that only exist synthetically. By the middle of the 1960s, there were more than 40,000 patients with mental illness engaged in psychedelic research studies and being treated in clinical settings with these synthesized drugs. The broader cultural tumult of the decade, however, led to a backlash; by the late 1960s regulators began to put many psychedelic substances (synthesized and natural) on restrictive "schedules" and to describe them as unsafe, with potential for abuse and harm.

The 1971 United Nations Convention on Psychotropic Substances classified psychedelics, including mescaline, LSD, DMT and psilocybin as Schedule I drugs, the level with the highest potential for abuse and no accepted medical use. In the US, the effect of this move was to prohibit psychiatrists from prescribing them and researchers from doing work in this area. Over the next two decades, research on psychedelics virtually stalled, and psychedelic use went underground.

The renewed interest, gradually growing since the 1990s, has been prompted by the persistence and growth of unmet need in mental health, and propelled in recent years by interest from regulators as well as from researchers. This has led to more stringent methods

in psychedelic research than previously existed. Studies conducted up until 1976 lacked consistency, control groups, statistical analysis, reporting of adverse effects, and blinded study teams. Today, researchers are required to adhere to specific and high standards under federal law and human subject protections for clinical trial research<sup>94</sup>.

Over the last three years, the FDA has awarded Breakthrough Therapy designation to three psychedelic research programs – one in MDMA (to MAPS – the Multidisciplinary Association for Psychedelic Studies in 2017) and two in psilocybin (to COMPASS Pathways in 2018 and to Usona Institute in 2019). Today there are a growing number of research studies exploring the use of psychedelic substances taking place around the world. Psilocybin therapy is gaining support in the medical research community as a highly promising innovation in the treatment of a variety of disorders including headaches, obsessive compulsive disorder (OCD), anxiety, addiction, eating disorders and depression. More than 20 clinical studies are currently underway to determine the therapeutic potential of psilocybin, as well as investigating its mechanism of action.

In 2019, two psychedelic research centers were established at major academic institutions: Imperial College London in the UK, and Johns Hopkins University in Baltimore in the US. The Medical University of South Carolina announced in February 2020 that they were planning a psychedelic research center, to open in mid-2021, and several additional academic psychedelic research centers are currently in development. Psychedelic research is returning to the mainstream.

Name	Context	Mechanism of action	Effects	State of research
Psilocybin	An active ingredient in so-called "magic mushrooms". Played a role in rituals and as medicine in indigenous populations in pre-Columbian Central and South America <sup>95,96</sup> . Naturally grows in 75 species of mushrooms across the world <sup>97</sup> . Has been synthesized for use in clinical trials	Psilocybin is a prodrug for psilocin. Psilocin is distributed throughout the body, including the central nervous system. Psilocin acts as an agonist at 5HT <sub>2A</sub> and 5HT <sub>1A</sub> receptors. Affinity has been reported at several serotonin receptors, reported here in order of affinity: 5-HT <sub>2</sub> , 5-HT <sub>2B</sub> , 5HT <sub>1D</sub> , 5HT <sub>6</sub> , 5HT <sub>5</sub> , 5-HT <sub>2C</sub> , 5-HT <sub>2A</sub> , 5HT <sub>1B</sub> , 5-HT <sub>1A</sub> , and 5-HT <sub>3</sub> <sup>98</sup>	Altered states of consciousness, dissolved sense of ego, enhanced empathy, sense of unity, insight, elevations in body temperature, pulse, respiratory rate, and systolic blood pressure <sup>99</sup> . Physiological effects return to baseline within 300 minutes <sup>99,100</sup>	Pilot studies (using synthesized psilocybin) conducted for OCD, existential distress, tobacco addiction, alcohol addiction and TRD. Ongoing clinical trials (mostly in phase II) for TRD, MDD, addiction, anorexia nervosa, anxiety, depression with mild cognitive impairment or early Alzheimer's disease, OCD, demoralization in long-term AIDS survivors, migraine and cluster headaches <sup>101</sup>
Mescaline	Active chemical component in peyote cactus, grown primarily in Central America. Used by indigenous groups for different types of meditation, religious practices and psychedelic therapy. Considered addictive. Not approved for any modern treatments <sup>102</sup>	Directly impacts the central nervous system, processed through the pancreas, liver, kidneys and spleen. Binds to serotonin receptors in the brain to produce various physical and psychological effects <sup>102</sup>	Elevated body temperature and heart rate, nausea and vomiting, dizziness, lack of coordination, altered perceptions of colors, sound and time, intense emotions and visuals, distorted sense of reality and an inability to concentrate <sup>102</sup>	No controlled studies for any specific indications <sup>102</sup>

#### Figure 3.1: Psychedelic compounds (psychedelic means "mind-manifesting")

Name	Context	Mechanism of action	Effects	State of research
Lysergic acid diethylamide (LSD)	Also known as acid. Initially designed to treat respiratory depression, evolved as an anesthetic and an aid in psychoanalysis in the 1950s <sup>103,104</sup>	Pleiotropic mechanism involves serotonergic, dopaminergic and glutamatergic neurotransmission. Actions mediated primarily through modulation of serotonergic signaling in the dorsal raphe (partial agonist at 5HT <sub>2A</sub> and full agonist at 5HT <sub>1A</sub> receptors <sup>105,106</sup> )	Lasting up to 12 hours, LSD alters perception for the senses: touch, sight and hearing. Increases heart rate, increased body temperature, increase blood pressure, dilates pupils <sup>107</sup>	Ongoing phase II trials for anxiety associated with life-threatening illness, cluster headache, anxiety symptoms in somatic disease and psychiatric anxiety disorders, major depression, and illnesses related to anxiety <sup>101</sup>
MDMA	Also known as ecstasy. Chemical compound designed to synthesize bleeding control medications <sup>108</sup>	May encourage communication and insight in psychotherapy sessions <sup>108</sup> . Increases levels of serotonin, dopamine and norepinephrine, resulting in increased emotional stimulation, sparking emotional memories and growing empathy and extroversion towards others <sup>108</sup>	Hypertension, dizziness, panic attacks, and in some cases loss of consciousness and seizures <sup>108</sup>	Phase III trial for treatment of PTSD. Phase I or II for alcoholism, fear extinction, anxiety with life-threatening illness <sup>101</sup>
Ayahuasca	Also known as yage <sup>109</sup> . Result of the combination of <i>psychotria virdis</i> and <i>banisteriopsis caapi</i> , both grown in Latin America. Potential therapeutic effects for mental illness and alcohol abuse <sup>109</sup>	The banisteriopsis caapi vine provides ayahuasca with a monoamine oxidase inhibitor, which prevents the metabolism, and therefore prolongs the actions of DMT. The DMT within ayahuasca has activity at serotonergic receptors, glutamatergic receptors, dopaminergic receptors, acetylcholinergic receptors, TAA, and sigma-1 receptors <sup>109</sup>	Produces powerful visual and auditory hallucinogenic experiences within 30 minutes of consumption and for several hours. Reduces activity in the brain and impacts serotonin levels, which can aid personal reflection on cognition, emotions and memories. Can induce intense vomiting, and, in some cases, cardiac arrest or seizures <sup>110</sup>	Phase II trial investigating antidepressant effects to treat major depression <sup>101</sup>

#### Psilocybin therapy

Synthesized psilocybin, the most researched psychedelic substance, is structurally similar to serotonin, a neurotransmitter presumed to have a role for the regulation of mood. In a similar manner to serotonin, psilocybin allows additional sensory information to reach a person's consciousness, resulting in perception changes<sup>111</sup>.

In contrast to many other Schedule I drugs, psilocybin is not considered addictive by experts. Furthermore, unlike standard antidepressant treatments where 95% of patients experience negative side effects, psilocybin is believed to have few negative side effects outside the therapy session. In early studies, it has shown signals of immediate results through episodic treatments<sup>112,113</sup>.

#### Psilocybin therapy protocol

Psilocybin therapy is a combination of a dose of synthesized psilocybin given in a controlled environment with the psychological support delivered by a specially trained mental health care professional before, during and after the psilocybin session. Psychological support sessions are considered an essential part of the treatment and are designed to ensure patient safety and optimal therapeutic outcomes.

Psychological support delivered in some clinical trials in the context of psilocybin therapy can comprise:

- **Preparation:** which aims to establish a therapeutic alliance between the patients and specially trained therapists, and to demonstrate/practice skills of self-directed inquiry and experiential processing which are important during the psilocybin session
- **Support during the psilocybin session:** in which therapy takes a non-directive approach. The therapist's role is to establish psychological safety and minimize anxiety to allow the patient to embrace the psychedelic experience and its potentially cathartic effects
- Integration: which helps the patient to process emotional and physical experiences, and insights gained during the psilocybin session

#### Psilocybin academic studies

The therapeutic potential of psilocybin in depressive and anxiety conditions has been demonstrated in a number of academic-sponsored studies over the last decade. In these studies, psilocybin, when administered in conjunction with psychological support, provided rapid reductions in depression symptoms after a single dose, with antidepressant and anxiolytic effects occurring on the day of administration and lasting up to the six-month follow-up period for a number of participants<sup>114-120</sup>.

Studies conducted at the University of California Los Angeles (UCLA), New York University, and Johns Hopkins University investigated the effect of psilocybin therapy in alleviating existential distress in patients suffering from advanced-stage cancer<sup>114</sup>. The first pilot study, published by UCLA in 2011, was conducted on 12 participants with anxiety related to advanced-stage cancer. Participants underwent two administration sessions spaced several weeks apart. In one session, each patient received synthesized psilocybin and in the other session each patient received a placebo (niacin), and the order in which they were administered was randomized. Depressive symptoms tended to improve, with significant reduction from mild to minimal depression at one and six months.

The second study, at New York University, published in 2016, investigated the efficacy of psilocybin to treat anxiety or depression related to cancer in 29 patients<sup>115</sup>. Similar to the previous study, participants underwent two administration sessions spaced several weeks apart, one with synthesized psilocybin and one in which they received placebo (niacin). Again, depressive symptoms tended to improve, with significant reduction from mild/moderate to normal/minimal depression up to six months.

The 2016 study at Johns Hopkins University compared low- versus high-dose of synthesized psilocybin treatment in 51 patients with anxiety or depression and life-threatening cancer<sup>116</sup>. Participants received either the low or the high dose of psilocybin first. At a second

administration session five weeks later, patients who had received the low dose first were given a high dose, whereas the high-dose first group were given a low dose of psilocybin. In the high-dose first group, psilocybin treatment resulted in significant reductions in measures of depression and anxiety at five weeks following the first session. These results were sustained at the six-month follow up. More than two thirds of patients described psilocybin therapy as among the top five most meaningful experiences of their lives, alongside the birth of a child or the death of a parent, six months after their psilocybin therapy session.

Imperial College London carried out an open label pilot study, first published in 2016, in which 20 patients with TRD were treated with a 10mg dose of synthesized psilocybin followed by a 25mg dose, one week later. The depressive symptoms of 19 patients who completed the study were assessed over a six-month period. A significant decrease in depressive symptoms was observed as early as one week after the psilocybin session, and sustained up to six months<sup>117,118</sup>. These preliminary results suggest that psilocybin therapy could be a transformational (or disease modifying) treatment, offering a rapid onset of action, and a sustained and prolonged relief of symptoms with only mild and transient side effects for patients with TRD.

Similar positive effects were reported in a study conducted at John Hopkins University and published in 2020, in participants with MDD<sup>119</sup>. Here, 24 participants were randomized into two groups. One group received treatment immediately after baseline, while a waitlist control group received treatment after an eight-week delay. Two doses of synthesized psilocybin were given to participants. Significant differences between the two treatment groups were observed in depression severity measures at one and four weeks after treatment, caused by a decrease in scores in the "immediate treatment" group.

In April 2021, the New England Journal of Medicine published results from an Imperial College study that compared the effects of two sessions of psilocybin therapy (using COMPASS Pathways' synthesized COMP360 psilocybin) with a six-week course of a leading SSRI antidepressant, escitalopram, in 59 people with MDD<sup>120</sup>. The study showed signals of positive activity in COMP360 psilocybin when compared with escitalopram and concluded that psilocybin findings should be explored further in larger studies.

#### Large-scale clinical trials

Psilocybin therapy using synthesized psilocybin is currently being explored for depression in two large-scale clinical trials. The first is a phase IIb dose-ranging multi-country, multi-center randomized controlled trial in 233 patients suffering with TRD, sponsored by COMPASS Pathways, a mental health care company. COMPASS was set up by George Goldsmith and Ekaterina Malievskaia in 2016 after they had experienced the frustration of watching a loved one suffer with mental health challenges. Along their journey to find help, they met many other patients and families who felt similarly frustrated and disempowered; they started COMPASS to improve patient experience and outcomes, and to transform mental health care. COMPASS's mission is to accelerate patient access to evidence-based innovation in mental health. Their first program is developing psilocybin therapy for TRD.

The second large-scale psilocybin study is a phase II single dose US-only trial with 80 MDD patients, funded by Usona Institute. Usona is a non-profit medical research organization dedicated

to supporting and conducting pre-clinical and clinical research to further the understanding of the therapeutic effects of psilocybin and other consciousness-expanding medicines.

#### Mechanism of action and therapeutic support

Researchers believe that psilocybin may acutely decrease activity within the default mode network (DMN), a system of functional connections in the brain that is responsible for introspection and planning. The DMN is formed and strengthened through adaptive responses to life events and experiences, and excessive rigidity of the DMN could cause symptoms of rumination, depression and other mental health conditions. The downregulation of the DMN by psilocybin may temporarily lead to increased connectivity between brain regions that normally don't communicate with each other, corresponding to the subjective experience of "egodissolution" and the subsequent generation of new perspectives and insights<sup>117</sup>.

Such experiences can be uncomfortable or anxiety-provoking. Extreme prolonged anxiety is colloquially referred to as a "bad trip" and results from a person attempting to maintain control over the experience and the integrity of unproductive patterns. The goal of psychological support during psilocybin sessions is to ensure the psychological safety of the patient by minimizing anxiety and encouraging openness to all emerging experiences. Basic safety, as measured by the level of anxiety, is the best predictor of clinically meaningful outcomes and durability of the response<sup>121</sup>. It has also been reported that connectivity changes within the DMN were predictive of outcome in patients with TRD at five weeks<sup>121</sup>.

In contrast to many other treatments and medicines, patient experience is critically important in psilocybin therapy. As noted above, in one study, more than two thirds of patients described psilocybin therapy as being among the top five most meaningful experiences of their lives, six months after their psilocybin therapy session<sup>116</sup>.

#### Creating accessibility for new treatment options

In addition to the FDA-approved clinical trials taking place with synthesized psilocybin as a drug product, there are currently several efforts underway across the US to decriminalize and legalize the purchase and use of psilocybin.

It is important to note that the synthetic psilocybin used in clinical trials today is manufactured and developed to strict regulations, known as Good Manufacturing Practices (GMP) and Good Clinical Practice (GCP) guidelines, allowing the FDA to confirm that any product that reaches patients with a diagnosed mental health illness meets the highest levels of purity, quality, safety and efficacy.

Psilocybin used outside clinical trials tends to be naturally occurring psilocybin found in a range of mushrooms, which often contain other active substances in unknown quantities.

#### Decriminalization

Psilocybin has now been decriminalized in Oregon, Ann Arbor, Denver, Oakland, Santa Cruz, and Washington, DC, and there are campaigns to expand this across the US in 2021. These measures are largely connected with recreational use of naturally-occurring psilocybin, which is very different from the medical model described above, where approved and regulated psilocybin therapy is prescribed to patients suffering with a mental health illness, and

synthesized psilocybin is given in a specially designed setting alongside psychological support from a specially trained therapist. While it seems sensible to suggest that people don't go to jail for possessing magic mushrooms, it is unlikely that decriminalization will do much to address the mental health crisis.

#### Legalization

A measure was passed in Oregon in 2020, going beyond decriminalization and allowing for the legal medical use of "psilocybin products" including magic mushrooms to treat mental health conditions in licensed facilities with registered therapists. A two-year development period is now underway.

Supporters of legalization argue that magic mushrooms have been used safely and effectively for thousands of years. However, caution has to be applied here. First, many patients with a diagnosed mental health illness suffer with one or more mental and physical co-morbidities and need to be carefully screened, assessed and supported by licensed healthcare professionals before they can be exposed to psychedelic therapies. Second, regulation is important for patients. It is needed to determine quality, safety, and efficacy - with evidence. This evidence does not currently exist at a level that would be acceptable for the FDA or any other medicine regulator to grant a license for the medical use of psilocybin therapy. The focus of the medical model is on ensuring that patients diagnosed with a mental health illness are appropriately screened and supported by licensed healthcare professionals. The questions we should be asking are: is the medicine safe; does it work (and if so, for whom); and can I trust that it is the same quality for every patient everywhere in the world?

The difference between an approved medicine and a psilocybin product or plant with medicinal properties, lies in the data generated in large-scale, rigorous clinical trials that enables a regulator to answer yes to all these questions. The small studies that were conducted in the 1960s and more recently in academic centers, are not suitable for regulatory approval because they were not designed for this purpose and do not meet the stringent requirements of today's clinical studies for drug development. The regulatory approval system has evolved over decades to ensure the producers of the medicine meet rigorous quality standards and are subject to inspections as long as they are on the market. This is one of the core roles of the FDA. Once a medicine has been approved by a regulator, it can be integrated into health systems and reimbursed – and only then does it have a chance of getting to patients suffering with a diagnosed mental health illness who might benefit from it, safely and quickly.

## Improving patient access, experience and engagement through technology and data

There is little doubt that technology has the potential to improve patient access to care, as well as quality and consistency of care. Telemedicine platforms and mobile applications have grown in popularity, enabling patients to access care remotely, as well as to order repeat prescriptions, and to monitor adherence to medication and side effects. A JAMA review of telemedicine service growth in commercially insured populations in the US found that 53% of telemedicine consultations identified were tele mental health interactions<sup>122,123</sup>. The trend has accelerated with the COVID-19 pandemic with a significant increase in tele mental health visits, ranging from +3,200% in 18-29 year olds to +6,900% for those over 70 years, according to a major US payer study<sup>124</sup>. This will have an impact in all fields of medicine, including psychotherapy. Patients can already engage with therapists online through video or text-based communication systems, or even interact with chatbots. Such solutions can break down logistical barriers as well as reduce stigma.

There are now more than 100 individual mental health online counselling (psychotherapy) venues, and over 40 online practice networks, offering a wide range of services, from confidential video calls with therapists to in-person session<sup>125</sup>. Some telehealth providers now guarantee a therapy session within five days of request, and allow patients to access and share their electronic health records<sup>126</sup>.

It is not surprising that a disproportionate number of new digital health technologies are being developed for the treatment and management of a wide range of mental health conditions<sup>127,128</sup>. More than 1,000 mental health start-ups were counted in a recent research study, growing at 100 a year in the US alone<sup>128</sup>. Venture investment in digital mental health solutions is (probably under-) estimated at \$600m in 2019, with a five-fold increase in the previous six years; and the 2019 CB Insight report highlighted mental health as the area in healthcare "most likely to be disrupted" in 2020<sup>129,130</sup>.

Several applications have become popular among individuals seeking to improve their mental health and wellbeing through mindfulness, education, peer-to-peer interactions and self-care practices, or helping with the management of medication or depressive symptoms. Some evidence-based digital mental health apps claim that they can alleviate stress, address mood disturbances, break unhealthy thought patterns, or simply boost self-awareness, leading to greater overall health and wellbeing - yet most digital mental health solutions do not provide robust evidence to support their claims<sup>131</sup>. It is therefore important to draw clear distinctions between health and wellness solutions designed to improve mental performance, those intended to maintain general wellbeing, and those focused on the treatment of mental illness.

As patients gain confidence in using digital mental health tools to access care, and understand and manage their conditions, they increasingly congregate in online communities to share their experiences and seek peer support. Online communities can help individuals suffering with depression feel less withdrawn and isolated, and better educated and connected; they can alleviate caregiver burden and reduce unnecessary face-to-face visits, bringing down the overall cost of care. Digital tools are beginning to be used to collect data on how patients feel and function, and to establish surrogate measures for clinically meaningful endpoints. These new digital biomarkers, based on real world data, when combined with underlying biological and genetic data, or data coming from medical research or medical records, can generate highly valuable research insights and hypotheses, as well as positive reinforcement loops that can activate sustained behavioral changes in patients' lives. Such datastreams, combined with rigorous research, will enable a more evidence-based, personalized, predictive and preventative mental health care model.

It is exciting to imagine a future where data from multiple sources is integrated into a personalized "mental health dashboard", from which individuals Technology opens untold opportunity for the future of behavioral health - especially in underserved areas by providing greater patient access, better experience and enhanced engagement. High-tech can still be high-touch if we are prudent and keep our care patient-centered. We are only scratching the surface of its potential.

> Chuck Ingoglia, National Council for Mental Wellbeing

can assess their mental health state in real time and take meaningful actions to achieve and maintain mental health wellbeing. Developments in virtual reality and technology-enabled neurocognitive enhancing techniques (sometimes referred to "neurobics"), as well as "digital therapeutics", ie evidence-based, regulated, reimbursed and prescribed software-based therapeutic interventions, are among the most exciting areas of research. Many think that these new treatment modalities will become the backbone or standard of care across a wide range of mental health conditions<sup>126</sup>. Mental health care is evolving to a multi-modal combination of online and offline support and care which could offer a superior patient experience, greater access, and better outcomes at a lower total cost.

It is encouraging to see the advances in medicine and technology that are emerging in the field of depression and other mental health conditions. These innovations could bring a muchneeded new model of patient-centered care to the millions who are suffering. But how do we ensure that promising research and development is translated into safe, effective, accessible and affordable treatments that can be delivered on a large scale? This will only have a chance of success if regulators, payers, healthcare professionals, researchers, developers, and providers, work together to bring this to patients.

# Part IV: A transformational approach to support innovation and improve outcomes

For the first time in decades, advances in medical research and in technology are offering new ways to treat patients with TRD and address a persistent and growing mental health crisis. The focus now has to be on how to ensure that these treatment options are rigorously researched and developed, and made available, accessible and affordable to all who might benefit from them.

## To ensure the broadest patient access to innovation in mental health, everyone involved in the mental health care system needs to work together to:

- 1. Stimulate research and entrepreneurship, and scale transformational solutions
- 2. Introduce more dynamic regulatory approval pathways
- 3. Measure and deliver the outcomes that matter to patients
- 4. Implement simpler and more effective reimbursement and payment models
- 5. Accelerate expansion of community mental health services
- 6. Expand and train the mental health workforce
- 7. Accelerate widespread adoption of digital technologies
- 8. Ensure that psilocybin therapy follows an evidence-based, medical route to patients through regulatory approval and adequate payer reimbursement

Significant systemic changes are needed across the entire mental health care system. Stakeholders need to work in close collaboration with one another, and with patients, to develop more patient-centric, evidence-based, and technology-enabled care models. These stakeholders include:

- Researchers
- Developers
- Healthcare professionals
- Patient groups
- Regulators
- Payers
- Provider organizations
- Employer purchaser organizations
- Faith-based organizations
- Consumer-based organizations
- Policymakers
- Employers
- Health data organizations

## 1. Stimulate research and entrepreneurship, and scale transformational solutions

Better funding mechanisms and incentives should be developed to support researchers and entrepreneurs who can deliver a step change in mental health care, eg with novel treatment modalities, new mechanisms of action, new digital technologies, new models of care. Research grants should be more easily accessible, transparent and flexible in scope. Today, grant allocation cycles are long and laborious, criteria upon which grants are allocated are not always clear, and there are often onerous conditions attached to the use of funds. Researchers and entrepreneurs must be allowed greater flexibility in deploying grant money as new evidence from their work emerges.

Evidence-based innovation in healthcare is often difficult to develop at scale. This is largely due to a fragmented system and excessively long decision-making cycles. Research efforts need to be efficiently translated into tangible and valuable solutions and adopted at scale. Incentives could be put in place to allow researchers to rapidly prototype, test and iterate such solutions in real world clinical settings to assess their real impact and value in patient care.

Organizations willing to innovate and shape the future of mental health care should be incentivized to dedicate more resources to experimenting and exploring breakthrough ideas that may not yield returns within a budget cycle or an established commercial paradigm.

## 2. Introduce more dynamic regulatory approval pathways

The failure to implement successful treatment options for depression stems in part from the complexity of the condition. Root causes are poorly understood, diagnostic criteria reflect a wide range of symptoms which are intrinsically subjective, and co-occurring conditions are highly prevalent. The current regulatory framework for depression relies upon consensus guidelines and expert opinions that do not adequately reflect clinical practice.

The lack of clear standards of care, and linear treatment algorithms in depression, create significant challenges in designing clinical trials that yield results that are generalizable. It would be helpful to have more flexible regulatory guidelines on trial design, more dynamic approval pathways, and a greater regulator-payer alignment<sup>132,133</sup>.

- Update criteria and guidelines for clinical trials more regularly to take into account improved understandings of depression. The FDA guidelines for MDD: Developing Drugs for Treatment were updated in June 2018, the first time since they were developed in 1977<sup>134</sup>
- Update outcome indicators. Treatment effectiveness is determined by established rating scales that may not capture the full extent of the benefits of new treatments, eg fast onset of action, quality of life and functioning, cognitive and emotional benefits, patient experience and preference
- Allow choice of active comparators. The lack of well-established standards of care for depression makes it hard to compare the relative efficacy and effectiveness of investigational drug candidates

- Provide greater support for adaptive approval pathways and the use of real-world data. This will accelerate time to market, with conditional approvals based on less clinical evidence and more real-world data to assess effectiveness and value
- Improve alignment between regulators and payers on evidentiary requirements. Regulators assess quality, safety and efficacy of a therapy in the context of carefully designed trials and controlled conditions. Payers, however, are interested in how clinical efficacy translates into cost-savings, budget impact, and cost-effectiveness in the real world. There is no harmonized method of assessing new technologies and whether interventions are good value for money. Sponsors of clinical trials (both large and small companies) are increasingly left with the impossible task of "squaring the circle" between regulators and payers, and across payer organizations to satisfy wide-ranging evidentiary requirements. Running a larger number of more sophisticated and organization-specific trials becomes cost-prohibitive and results in a delay of patient access to transformational innovation. A substantial effort is needed to set up formal early scientific advice processes, possibly run in parallel or even jointly by the FDA and payer organizations. Such processes should be focused on offering feedback and guidance on evidence generation plans, clinical trial design, and optimal pharmacoeconomic approaches. Several Health Technology Assessment bodies in Europe (HTAb) already offer such processes independently and in collaboration with European and national regulators135,136

## 3. Measure and deliver the outcomes that matter to patients

For all the talk about patient-centricity, research and development efforts are still largely driven by the need to satisfy evidence requirements needed for approval and reimbursement. We need to understand what matters to patients and their caregivers; what we study and the outcomes we measure need to be relevant and meaningful to patients as well as to clinicians, regulators and payers. This can begin with more dialogue with patients themselves, through forums or patient groups and associations. For example, the recently published Depression and Bipolar Support Alliance (DBSA) Report of the Externally-led Patient-Focused Medical Product Development Meeting on Major Depressive Disorder highlighted "Peer-desired outcomes go beyond surviving. Peers seek the opportunity to thrive<sup>137</sup>.

No other company or industry would survive without satisfying, even delighting, customers, and healthcare should be no different. Stakeholders across the healthcare value chain, particularly in mental health care, can still get away with delivering sub-optimal solutions, because of the massive information asymmetry between providers, industry and patients which feeds off a complex, fragmented and opaque system. However, greater access to information, more advanced technologies and healthcare reform are rapidly empowering patient consumers and putting pressure on organizations to adapt their models.

## 4. Implement simpler and more effective reimbursement and payment models

Broad patient access to innovation will always depend on appropriate insurance coverage and reimbursement. More flexible payment models to support new care models need to be developed. Reforms to move from a volume-based (fee for service) framework to a value-based (pay for outcomes) one, are underway, but not proceeding quickly enough, given the urgent unmet need in mental health.

Industry and payers need to agree how to ensure the risk is evenly distributed, and how to develop the infrastructure to collect high quality real-world data to measure agreed outcomes on a large scale. A balance between longer-term, population-focused capitated reimbursements models, and a patient-centric and technology-enabled approach needs to be struck. Shared savings schemes are appealing but require an agreed upon measurement of the total cost of care. Bundled payment approaches linked to episodes of depression are welcome but demand an alignment of what constitutes an episode of care in the context of a chronic condition. Partnership between payers and industry on running expanded access trials are promising but require a clear articulation of what success looks like and long-term commitments.

## 5. Accelerate expansion of community mental health services

In recent years, we have observed a positive shift in mental health care delivery from acute to primary and community-based care. Results have been so encouraging that the US government has requested an investment of almost \$1bn for the expansion of a Certified Community Behavioral Health Centers (CCBHCs) demonstration program in its Fiscal Year Budget Request 2021<sup>138</sup>. The Substance Abuse and Mental Health Services Administration (SAMHSA) has since released a list of 134 clinics that were awarded a Certified Community Behavioral Health Clinic (CCBHC) Expansion Grant, expanding the program to include 340 CCBHCs across 40 states, Guam, and Washington, D.C<sup>139</sup>.

We urge all parties involved to embrace the government's request to continue investing in expanding, integrating and upgrading community mental health centers, particularly CCBHCs, to more states across the US. These should be appropriately staffed, equipped and certified to offer a full range of behavioral services and safely deliver novel therapeutic interventions, like psychedelic therapies, that require observation and monitoring.

We should also consider greater integration of primary and behavioral health care, with the inclusion of more mental health providers either directly in the practice or virtually, working as part of the team.

### 6. Expand and train the mental health workforce

There is clearly a shortage of healthcare professionals available and equipped to deal with the growing mental health crisis. Numbers aside, new treatments and therapies often require a change in infrastructure, technology and methods. Psilocybin therapy, for example, needs to be delivered in a controlled environment, under the supervision of specially trained therapists. Many US psychologists and psychiatrists are self-employed, mainly as private practitioners and independent consultants, and work in small practices which are unlikely to be set up to deliver new and different treatments.

To establish new treatments and therapies and make them accessible to patients, healthcare providers need to be educated, trained and certified. This means working with academic institutions and integrating new methods into academic curricula. Comprehensive educational programs need to be put in place to educate a wide range of healthcare providers on the evidence base and value of psychedelic therapies. Ad-hoc facilities need to be developed and existing infrastructure will need to be adapted. Other therapies may have similar structural and staffing requirements, and consideration should be given to making it easy to develop and open adequately equipped centers.

## 7. Accelerate widespread adoption of digital technologies

Healthcare is a laggard in embracing digital transformation at scale. In many aspects of healthcare delivery, human interaction is essential and should remain the gold standard. However, we know that technology could potentially play a significant role in improving the way in which patients with depression access and experience mental health care.

Telepsychiatry can play a key role in complementing and augmenting face-to-face visits, and bears huge potential to improve access to care, especially in rural areas and for the underserved populations, be it to emergency departments, integrated care services or other; and we call for more private and public investment and healthcare policies to incentivize and reimburse a broader range of evidence-based mental healthcare services delivered remotely<sup>140</sup>.

Imagine a world in which a patient with TRD could talk to their doctor without leaving the house, eliminating travel difficulties as well as the need to live in an area with good mental health provision. They could access support groups and talk to other patients through online forums. After treatment, information on their behaviors could be captured through their smartphone and transmitted directly to a healthcare professional watching out for signs of relapse. Patient data, collected carefully and with due concern for privacy, could be aggregated to provide patients with specific and personalized advice and used to develop real-world evidence to inform further research. Much of this is starting to happen today. But it needs to be expanded rapidly and delivered on a large scale, if it is to begin to have a broad enough impact.

The greatest barriers to widespread adoption of innovation are usually not related to lack of evidence of its benefits but are more cultural and organizational. To overcome such barriers, provider and payer organizations should dedicate and ringfence enough resource (financial and organizational) to invest in technologies, acquiring or partnering early-stage innovative companies and dedicating sufficient time and resources to scale up promising innovations after successful proof of concepts are completed.

By embracing digital mental health solutions, we can finally take mental health care into the 21st century.

### 8. Ensure that psilocybin therapy follows an evidencebased, medical route to patients through regulatory approval that facilitates patient access

There is an increasingly vocal campaign to introduce legalized psilocybin therapy through licensed facilities in the US. Legalization of psilocybin mushrooms in this way carries a high level of risk and is unlikely to meet the needs of the majority of patients suffering with TRD.

Drug therapies are reviewed and approved by medical regulators, such as the US FDA, providing the assurance that they have been subjected to extensive clinical trials and have generated evidence to show safety, efficacy, and quality. The psilocybin used in clinical trials is synthesized and subject to the highest medical regulatory standards. Clinical evidence and regulatory approval are also prerequisites for any reimbursement consideration. This means the medical route is the safest way to get psilocybin therapy, if approved, into the US health system, reimbursed, and made available to patients diagnosed and suffering with a mental health illness who might benefit from it, regardless of their ability to pay.

The FDA's Center for Drug Evaluation and Research (CDER) has recently established a Controlled Substance Program which aims to minimize risks associated with problematic use of controlled substances while enabling appropriate access for medical use<sup>141</sup>. This is a welcome move and CDER needs to work closely with industry and other stakeholders on policy around psychedelic drugs.

## Conclusion

In the time it has taken to read this paper, 92 people will have died from suicide, and another 1,841 people will have attempted suicide.

This paper sets out the urgency of the mental health crisis. Too many people are suffering with severe mental health conditions, like treatment-resistant depression, with little hope of any relief. This has an enormous impact on families, friends, colleagues, employers, and society at large.

Progress is being made. There are promising new therapies for TRD coming through clinical trials for the first time in decades. But significant change in the mental health care system is needed if this innovation is to reach everyone who might benefit from it.

Researchers, regulators, payers, providers, industry - and all stakeholders involved in mental health care - need to work in close collaboration with patients and patient groups to develop new care models that are truly patientcentric, evidence-based, outcome-focused, and technology-enabled.

The 21st century is already two decades old. It is time to ensure that our mental health care system is fit for purpose - providing care that is effective, accessible and affordable to everyone in need.

# Appendix A – Mood disorders and types of depression

Symptoms of mental illness differ across disorders, but also overlap in many cases. The heterogeneity of mental illnesses poses challenges for accurate diagnosis. The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), helps categorize and define mental health disorders to improve diagnoses, treatment and research. Below are the diagnostic criteria for MDD from the DSM-5.

#### Depression DSM-5 diagnostic criteria

The DSM-5 outlines the following criterion to make a diagnosis of depression. The individual must be experiencing five or more symptoms during the same two-week period and at least one of the symptoms should be either (1) depressed mood or (2) loss of interest or pleasure.

- 1. Depressed mood most of the day, nearly every day
- 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
- 3. Significant weight loss when not dieting, or weight gain, or decrease or increase in appetite nearly every day
- 4. A slowing down of thought and a reduction of physical movement (observable by others, not merely subjective feelings of restlessness or being slowed down)
- 5. Fatigue or loss of energy nearly every day
- 6. Feelings of worthlessness or excessive or inappropriate guilt nearly every day
- 7. Diminished ability to think or concentrate, or indecisiveness, nearly every day
- 8. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

To receive a diagnosis of depression, these symptoms must cause the individual clinically significant distress or impairment in social, occupational, or other important areas of functioning. The symptoms must also not be a result of substance abuse or another medical condition.

In addition to patient burden, caregivers who provide care for family members with a psychiatric illness are also at potential risk for burden and consequent decrease in overall health status. Some studies show multiple consequences of caregiver burden, such as:

- I. Mental health problems (eg depression, anxiety, stress, and burnout syndrome)
- II. Physical health deterioration (eg diabetes)
- III. Other negative effects (eg family dysfunction, social isolation, excessive use of health services, and financial problems)

Evidence also indicates significantly higher scores of overload in caregivers of psychiatric patients when compared with other conditions, such as other chronic diseases<sup>142</sup>.

## Appendix B - Summary of key facts\*

#### Major depressive disorder (MDD):

- More than 320 million people globally suffer with MDD
- In the US, about 17 million adults and three million children aged 12 to 17 years had at least one depressive episode in 2019
- One in five adults will experience a depressive episode at least once in their lifetime
- Approximately 90% of individuals who die from suicide in the US have an underlying mental illness, and about half of those suffer with MDD

#### Treatment-resistant depression (TRD):

- Depression that isn't helped after two or more adequate treatments for MDD is labelled as TRD
- About five million people in the US have TRD; there is a 20-30% prevalence of TRD among MDD patients
- About half of TRD patients are unable to perform daily tasks and experience a much lower quality of life
- Employment rates for TRD patients range from 55% to 63%, compared with an employment rate of 76% for those without a mental health illness
- Co-occurring mental and physical disorders are more common in TRD patients than in non-TRD MDD patients
- TRD carries 2-3x the medical costs of a non-TRD MDD patient, and suicide rates are 7x higher for TRD patients compared with non-TRD MDD patients

#### Mental health care spending:

- Annual overall spending on mental health care in the US is roughly \$200b around 5% of total healthcare spending
- Between 1986 and 2020, expenditure on mental health grew from \$32b to \$238b, a 650% increase
- On average, the healthcare-related cost of treating a TRD patient is around \$17,000-25,000 a year

#### Unmet need:

- Despite the amount of money being spent, there is significant unmet need
  - The numbers of people suffering with MDD (320 million worldwide) and TRD (100 million worldwide) are increasing
  - Every 40 seconds, someone in the world dies from suicide nearly 800,000 people every year. And in those 40 seconds, 20 more people attempt suicide
- More than a third of US patients with depression do not receive any mental health care
- Patients suffering with depression currently have two main treatment options: psychotherapy (also known as talk therapy) and antidepressants
- Medication provides some relief to many but doesn't work well for up to 50% of MDD patients

and can deliver significant side effects

- Only 29 active substances have been approved by the FDA for MDD since 1959
- Trial initiations for new therapeutics are down 50% over the last decade, and MDD drug candidates represent only 0.2% of the global drug pipeline

#### Psychedelic therapies: a new frontier

- Over the last three years, the FDA has awarded Breakthrough Therapy designation to three psychedelic research programs one in MDMA (to MAPS, the Multidisciplinary Association for Psychedelic Studies in 2017) and two in psilocybin (to COMPASS Pathways in 2018 and to Usona Institute in 2019).
- More than 20 clinical studies are currently underway to determine the therapeutic potential of psilocybin, as well as investigating its mechanism of action
- There are currently two large-scale clinical trials for psilocybin therapy
  - A phase IIb dose-ranging multi-country, randomized controlled trial in 233 patients with TRD, sponsored by COMPASS Pathways, due to report data in late 2021
  - o A phase II single dose US-only trial with 90 MDD patients, funded by Usona Institute
- In April 2021, Imperial College London published the first-ever study comparing antidepressant treatment with psilocybin therapy, in 59 patients with MDD. The study showed signals of positive activity in COMP360 psilocybin when compared with escitalopram, and concluded that psilocybin findings should be explored further in larger studies

"COVID has impacted our mental health, but it is also opening up more conversations about mental health. It is clear that we need to do more to help those who have run out of options, and to transform mental health care on a large scale."

George Goldsmith, CEO & Co-founder, COMPASS Pathways

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